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Invited Perspective: Causal Implications of Gene by Environment Studies Applied to Gulf War Illness

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The thirtieth anniversary of the 1991 Gulf War has just passed, and much knowledge has been gained about the etiology and pathobiology of Gulf War Illness (GWI) over this time.[1,2] However, questions still remain about the exact causality of this chronic multisymptom disorder that affects an estimated 250,000 veterans.[3] Gulf War veterans had a unique constellation of exposures to nerve gas agents, pesticides, and other toxicants during the war that have been associated with the disorder.[4,5,6] Despite all the work that has been done, questioning of the evidence for a causal role of environmental exposures in GWI persists, driven in large part by the difficulties with conducting epidemiology studies of the role of environmental exposures during the Gulf War.[7,8] Furthermore, it has remained less clear why some veterans developed the disorder, whereas others with similar exposures did not. The analysis of gene by environment interactions with Gulf War exposures, as the study in the current issue of *Environmental Health Perspectives* by Haley et al. has done,[9] may help address these issues.

Chief among the issues raised about Gulf War epidemiology studies are selection biases in the study populations and recall bias given the frequent use of self-reported exposures, and of course confounding is always a concern. The study by Haley et al.,[9] offers some powerful arguments for causality that follow from their exploration of the interaction between self-reported exposure to nerve agents (as estimated by reports of hearing nerve agent alarms) and PON1 genotype in relation to GWI. PON1 is a known genetic determinant of susceptibility to organophosphate cholinesterase-inhibiting chemicals, including nerve agents; thus, if nerve agent exposure is a cause of GWI, the relation between nerve agent exposure and GWI would be expected to differ by PON1 genotype.

Haley et al.[9] report a significant interaction between PON1 genotype and hearing nerve agent alarms on the odds ratio for GWI. It has been shown that under the assumption of gene and environment independence (seemingly a reasonable assumption here and in fact borne out by the authors' analyses in the controls), an observed gene–environment interaction implies that, even in the presence of unmeasured confounding, a true interaction exists, either with the exposure of interest or with the unmeasured confounder[10]—in this case, something that would correlate with the occurrence of the nerve agent alarm sirens. Further, the authors conducted sensitivity analyses to explore the likelihood of unmeasured confounding over a wide range of plausible associations between an unmeasured confounder and the exposure or outcome, which suggested that such unmeasured confounding was quite unlikely to account for the interaction.

The concern over recall bias for a self-reported exposure has been a hard criticism of GWI research to address. However, here the authors conducted several quantitative bias analyses (QBA)[11] that covered a wide range of plausible bias parameters, which suggested that this could not account for the observed interaction. It is important to note that the QBA that explored a much-reduced specificity among the cases corresponds to the scenario of specifically GWI cases overreporting their exposures (increased false positives for exposure)—a primary concern of recall bias that certainly does introduce bias away from the null for the main effect of an exposure. However, it is different for a gene–environment interaction. As the authors' QBA analyses showed, as the exposure specificity was reduced, the interaction effect estimate in fact increased, suggesting that, if anything, the observed interaction was biased toward the null compared with the true interaction.

Not addressed by the authors, but another advantage endowed by the exploration of a gene–environment interaction, is an argument against selection biases in forming the study population. This too has been a criticism of GWI research that has been hard to counter. However, prior work has shown that even in the presence of selection bias in case–control studies (selection jointly on exposure and outcome), the odds ratio for a gene–environment interaction is not biased under the assumption that genotype does not influence participation conditional on exposure and disease status.[12] That the PON1 gene does not affect a complex behavior like participating in a study seems a plausible assumption to make.

In summary, the authors' exploration of a gene–environment interaction between presumed nerve agent exposure and the PON1 gene offers some strong arguments that there is a true causal effect at work. This exploration has important implications for how we think about the role of the environment in GWI. It also suggests, at least in part, why some soldiers who were presumably exposed to toxicants like nerve agents suffer from GWI and some do not. It is important to note, though, that these results do not rule out that the exposure alone could cause GWI, only that the same arguments for causality of the gene–environment interaction do not apply to the main effects. However, perhaps the presence of a gene–environment interaction increases suspicion that the environmental exposure on its own may have some effects as well. Of course, the kinds of causal inference challenges that exist in GWI research are often seen in other areas of environmental health research. The kinds of causal inference advantages described here in the exploration of gene–environment interactions—actually, any interaction, but the assumptions of independence of the interacting factors and that one of them does not drive things like participation are perhaps more often plausible with genetic variants—are equally applicable in many other settings and should be recognized and put to broader use by environmental health scientists.

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